**Zinc treatment prevents neutrophil recruitment and inflammation by blocking *Candida albicans* Pra1 during vulvovaginal candidiasis**

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Vulvovaginal candidiasis (VVC) affects around 75% of all women at least once in their life and 8% develop a recurrent form (rVVC), that substantially reduces the quality of life.
In this vaginal disease, *Candida albicans* triggers a non-protective influx of neutrophils, which are unable to resolve the infection and results in aggressive local inflammation and symptomatic disease.
Pharmacological control of VVC episodes and rVVC, although possible with maintenance antifungal therapy, remains problematic and does not eliminate the risk of both future re-infection and development of antifungal resistance.

The aim of our study was to investigate the role of the zincophore Pra1 in VVC immunopathology and its modulation with zinc.
Pra1 is a secreted *C. albicans* zinc binding protein released during zinc limitation and used by the fungus to forage for this essential micronutrient from the environment.
*In vitro* tissue culture systems, a mouse model of vaginal candidiasis and vaginal samples from patients with VVC/rVVC were used to evaluate the expression and role of *PRA1* in VVC immunopathology. In these systems, the modulation of Pra1 and the associated inflammation were also evaluated by the direct administration of a low amount of zinc.

Our results show that *C. albicans* Pra1 directly induced neutrophil migration and inflammation. Interestingly, *Candida glabrata*, which has lost the *PRA1* gene during its evolution fails to recruit neutrophils and heterologous expression of the *PRA1* gene *C. glabrata* promoted neutrophil chemotaxis.
We found that Pra1 is expressed by *C. albicans* at both neutral and acidic pH during vaginal epithelial infection and that expression was repressed by the addition of zinc.
Robust *PRA1* expression was also observed in clinical vaginal samples and a strong correlation between *PRA1* expression and levels of the neutrophil-activating cytokine IL-8 was found. In an experimental murine model of VVC, *PRA1* is expressed and the deletion of *C. albicans PRA1* abrogated inflammation, including neutrophil recruitment, IL-1β and MIP-2 production, without affecting fungal burden. Zinc treatment of *C. albicans* wild type infected mice downregulated *PRA1* expression and prevented inflammatory cytokine production and neutrophil infiltration.

These data demonstrate that the zincophore Pra1 is expressed during VVC and can act as a potent neutrophil chemoattractant molecule, driving inflammation in a self-amplifying inflammatory cycle.
For this reason, Pra1 can be considered a perfect target for blocking the symptoms of VVC and we demonstrate that his can be achieved with low levels of zinc supplementation.